The alveolar carbon monoxide uptake fraction: a simple, alternative measure of carbon monoxide transfer

R. Ameratunga, E.A. Harris

ABSTRACT: The measurement and interpretation of "diffusing capacity" by either single-breath or steady-state methods are complicated by both technical and conceptual difficulties. The CO uptake fraction is less complex but, as originally described, it is unacceptably sensitive to dead-space ventilation. A modification (the "alveolar CO uptake fraction", UA) largely removes this factor. We have measured UA in thirteen healthy subjects and 100 patients with a variety of pulmonary disorders. It is reproducible and appears sensitive to clinical abnormality. Its technical and interpretative simplicity suggest its use as an alternative to other measures of CO transfer.

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The single-breath method [11] for measuring pulmonary diffusing capacity (transfer factor) for carbon monoxide (Dco) is in general clinical use. Recently the American Thoracic Society published draft recommendations of an expert panel [1] for a standard technique. This report will illustrate the prevailing lack of agreement about how Dco should be measured and the numerous technical details which call for careful attention. Most of the important difficulties in both technique and interpretation arise from the wide gaps which exist between theory and clinical reality. Chief among these is the theoretical requirement of a homogeneous lung when, in practice, inhomogeneity must be assumed.

We have reviewed [7] the effects of non-uniform distribution of ventilation, perfusion and diffusing capacity on measured Dco and steady-state diffusing capacity. These effects may be considerable; even more importantly they may, acting together, alter the measured Dco or Dco, in opposite directions, one factor opposing another. This, together with purely technical problems, may account for much continuing uncertainty as to how a measurement of Dco should be interpreted. In the case of Dco the effect of non-uniformity is even more obvious [7] and this measurement has been almost abandoned.

Graham, Cottrell et al. [4, 5, 6] have recently developed a computerized model which takes account of many of the disturbing factors in the Dco method. This important work seeks to circumvent the difficulties but does not eliminate them.

In 1952, Bates [2] introduced the CO uptake fraction; this is simply the steady-state CO uptake expressed as a fraction of the CO inspired during the same period. It is given by:

\[ U = \frac{1 - F_{\text{ECO}}/F_{\text{ICO}}}{F_{\text{ICO}} - F_{\text{PICO}}} \]  

where Fe and Fi are expired and inspired concentrations. The Nt fraction in equation (1) merely corrects FeO for the effect of the respiratory quotient as in the case of Fio2 in calculating O2 uptake. U is a simple transfer function (fig. 1) which calls for no assumptions about pulmonary uniformity. It has not found favour as a measure of CO transfer partly because it is greatly influenced by dead-space ventilation (fig. 1) and thus by respiratory frequency, and partly because Dco and Dco are still widely supposed to measure true diffusing capacity.

The dead-space effect on U may be conceptually removed by considering UA, the alveolar uptake fraction, in which CO uptake is expressed as a fraction of the inspired CO reaching the alveoli. The effects of non-uniformity on UA are much less complex [7]; (see Discuss-


Alveolar single measurements of each of different days, are included in figure 2 respectively referred to the pulmonary laboratory in whom a additional healthy subjects, also studied repeatedly on open volumes were normal in all of them. Data from four patients signify chronic airflow obstruction not definitely classifiable as dominantly bronchitis. Nine healthy, non-smoking members of staff with this index in patients with pulmonary disease, using the normal predictions mentioned above.

In the present paper, we consider within-subject reproducibility of UA, back-pressure effects and experience with this index in patients with pulmonary disease, using the normal predictions mentioned above.

Methods

The investigation was approved by the hospital's Ethics Committee. Nine healthy, non-smoking members of staff volunteered for the study of reproducibility and back-pressure effects. Spirometry and plethysmographic lung volumes were normal in all of them. Data from four additional healthy subjects, also studied repeatedly on different days, are included in figure 2.

For the clinical study, we have analysed the results of single measurements of each of 100 patients consecutively referred to the pulmonary laboratory in whom a firm diagnosis of pulmonary disease had been made. Thirty patients had chronic airflow limitation (CAL). Nine of these had dominant dyspnoea on exertion, much increased residual volume, poor or no response to salbutamol aerosol and overinflation as judged radiologically, with or without visible bullae. They were considered to have emphysema. Of those remaining, twenty one patients either had dominant bronchitis (productive cough for at least three months of the year for at least two years) or their classification was in doubt. Twenty-two patients had sarcoidosis, proven by transbronchial, carinal or lymph-node biopsy. Of these, nine had no X-ray evidence of parenchymal pulmonary involvement but had bilateral enlargement of hilar nodes. Forty patients had interstitial pulmonary disease, either cryptogenic fibrosing alveolitis or due to rheumatoid disease, systemic sclerosis, polymyositis, systemic lupus, pulmonary eosinophilia, allergic alveolitis, asbestos, radiation or drugs (amiodarone, bleomycin). Eight patients had asthma.

Procedure

The subject, usually supine (four of the patients sat), breathed a mixture of approximately 0.07% CO in air from a 500-l Douglas bag through a Hans-Rudolph valve. Expired gas passed via an 8-l mixing-chamber through a dry gas-meter (Parkinson-Cowan CD4) from which litre increments were registered on a Post-Office counter. Breaths were similarly counted from the pressure swings within the breathing valve, measured by a differential manometer. Gas was sampled just downstream from the mixing-chamber and analysed for CO (Mijnhardt, infrared), CO2 (Datex, infrared) and O2 (Servomex, paramagnetic) before being returned to the system further downstream. Concentrations, expired volumes and breaths were noted every minute. CO concentration was always stable within 4 min. Data from the 5th to 8th min inclusive were averaged and used in the calculation of UA by equations (1) and (2). In the reproducibility studies, the procedure was prolonged to 16 min, giving two additional 4-min data-collection periods. In all cases tidal volume, frequency and ventilation rate were within the ranges seen in the subjects from whom UA predictions were derived [8]. In the supine position, between-subject variation is less than when sitting, in health [8].

Calculations

Oxygen consumption (\(\dot{V}O_2\)) was calculated conventionally. Fractional CO uptake was calculated from equation (1) and UA from equation (2). Prediction equations for UA [8] have the general form

\[ UA = a + b(\text{age}) + c(\text{height}) + d(\dot{V}O_2) + e(V_e - V_d f) \]

A predicted value thus varies with the prevailing \(\dot{V}O_2\), \(V_e\) and \(f\). The absolute magnitude of either measured or predicted UA is of little interest, but the difference between them, expressed in units of the appropriate standard deviation about regression, allows an estimate to be made of the degree of abnormality. When only low values of UA are of interest, single-sided confidence intervals are appropriate. Arbitrarily we define mild, moderate and severe abnormality as...
Reproducibility of alveolar carbon monoxide uptake fraction (UA) in nine healthy supine subjects.

<table>
<thead>
<tr>
<th>Sample period</th>
<th>5-8</th>
<th>9-12</th>
<th>13-16</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>0.0077</td>
<td>-0.0138</td>
<td>-0.0228</td>
</tr>
<tr>
<td>Day 2</td>
<td>0.0028</td>
<td>-0.0118</td>
<td>-0.0193</td>
</tr>
<tr>
<td>Means</td>
<td>0.0053</td>
<td>-0.0128</td>
<td>-0.0210</td>
</tr>
</tbody>
</table>

Analysis of variance:
Within-subject SD between days: 0.0320
Decrease across sample periods: p<0.005

Results are shown as mean differences (UA) from the predicted mean normal value. See text for further details.

healthy people should lie.

Results
Table 1 shows mean deviations for nine healthy supine subjects and three successive sample-intervals (5-8, 9-12 and 13-16 min) on two different days. Suppose that in a given sample-interval a subject had a measured UA of 0.843 and a predicted UA of 0.871, the deviation measured minus predicted is then 0.028. For the period 5-8 min, the grand mean was +0.0053, sufficiently close to the expected value of zero in healthy subjects. Between days the within-subject standard deviation (sd) was 0.032. This compares with a sd about regression of 0.046 (men) and 0.052 (women) for the normal supine prediction [8].

Across sample periods, UA progressively diminished, relative to the predicted value, and by analysis of variance this was highly significant (p<0.005). The obvious explanation is an increasing back-pressure effect from the pulmonary capillary blood as CO is progressively absorbed. Reasonable assumptions about blood volume [10], with measured haemoglobin concentration and absolute CO uptake each minute, allow calculation of the increase in HbCO saturation during the 9th to 16th min inclusive. This may be compared in each subject with the mean fall in UA relative to the predicted mean value. Such calculations showed UA diminished by roughly 0.015 for every 1% increase in HbCO saturation.

Figure 2 shows measured UA in subjects, scaled in sd units above or below the predicted normal mean value. The lower, single-sided 5.1 and 0.1% confidence limits are taken at 1.7, 2.5 and 3.6 sd respectively, corresponding with the 20 degrees of freedom which apply to the prediction equations [8]. All thirty one measurements in thirteen healthy subjects lie above the 5% limit. Two of eight asthmatics gave an abnormal result but all five whose forced expiratory volume in 1 s (FEV1) was at least half the predicted value [13] had normal UA. All nine patients with clinical emphysema had abnormally low UA, four of them below the 0.1% limit. Five of twenty one patients with CAL but without convincing criteria of emphysema had normal UA; the rest were abnormal, but UA was not obviously correlated with FEV1. In all but four of forty patients with non-sarcoid interstitial disease, UA was abnormally low, and grossly so in sixteen. Normal results were obtained in one patient with cryptogenic fibrosing alveolitis (p=0.063), two with collagen disease (p=0.100 and 0.190) of whom the first became abnormal one month later, and one with allergic alveolitis (p=0.543). All nine patients with sarcoidosis who showed no X-ray evidence of lung involvement had normal UA, six of the remaining thirteen were abnormal.

Discussion
There is now abundant theoretical [7] and practical [1] evidence that UA is an unsatisfactory measurement. It is appropriate to consider what requirements should be met by an alternative.

Firstly, it should be clearly interpretable, in the sense that a departure from normality has defined meaning. This requirement has been so badly met by both Dmax and Dmin that some have questioned the clinical value of any measurement of CO transport [3]. We showed [7] that a reduction in UA signifies, in principle, a low total diffusing capacity (in which we must now include gas-phase diffusion), mismatching of ventilation with respect to diffusing capacity, or both. Each can only reduce UA, whether acting alone or in combination. The third determinant, alveolar ventilation, is allowed for in the predicted normal UA with which a measured value is compared. UA is unaffected by ventilation/perfusion or ventilation/volume mismatching, sequential emptying or series inhomogeneity in the expired part of the alveolar gas.

Experimental proof of these statements is impossible to obtain. Even a comprehensive knowledge of a lung's gross and microscopic structure, far less the fragmentary insight available during life, does not allow any certain inference as to how that lung transports gases. Nor would it help to compare UA with Dmax in the same patients. Neither is an absolute standard by which the other can be evaluated, and in the event of disagreement it would be impossible to conclude that one was 'true' and the other 'false'.

On the other hand, if the theoretical argument is accepted, the meaning of an abnormal UA is considerably less complex than that of an abnormal Dmax and the interpretation of the results in our patients is straightforward. Concern is most likely to arise from our finding of an abnormal UA in many patients with 'bronchitis'. Some of these patients probably had significant emphysema. Others can be explained on the grounds of uneven ventilation with respect to diffusing capacity. This is the only likely explanation in our patients with asthma, in whom abnormal UA was associated with marked airflow obstruction. It appears that grossly abnormal UA is largely confined to clinical emphysema and interstitial disease, but in the last analysis neither UA nor Dmax can distinguish diffusive from distributive defects, however these are caused. We believe that the clinical advantage lies with UA because it is affected by fewer variables and always in the same direction [7].

An acceptable index should be reproducible yet sensitive to real changes. Our results show that UA is
reproducible to well within the 95% confidence limit of the prediction (table 1). Healthy subjects give results which are closely grouped above this limit (fig. 2). A within-subject $s_{0}$ of 0.032 corresponds to a difference between duplicates on different days of 0.045 ($i.e., s_{0} 	imes 2$). The mean measured $U_{A}$ in healthy subjects was 0.915, of which the duplicate difference is less than 5%. This compares with the 5 to 6% recommended maximum tolerance for duplicate measurements of $D_{o}$ made at the same session [1].

Sequential measurements of $U_{A}$ are sensitive enough to show clearly the effects of CO back-pressure, indicating its ability to detect small changes (table I). None of the data reported here were corrected for back-pressure. Since the prediction equations [8] relate to the 5-8 min sample interval in non-smokers, no correction is necessary if the starting carboxyhaemoglobin concentration is negligible. In many patients, this is not the case, and in these a back-pressure correction of $U_{A}$ is obviously practical. Our rough estimate of its magnitude awaits confirmation by direct measurement. Since the present study was completed, measurement in twenty subjects has given an average correction of 0.018, near to the present estimate of 0.015 (unpublished observations).

Finally, a functional index should be simply obtained with a standard procedure and minimal room for errors of measurement. $U_{A}$ fulfils these requirements. Its measurement is much simpler, and calls for less expensive equipment, than that of $D_{o}$. The procedure is, however, more prolonged. Our standard 8-min test could be shortened, perhaps to 5 min, but this is still much longer than that required for $D_{o}$. Absorption of CO is also greater in the $U_{A}$ procedure and serial tests on the same day would require correction for back-pressure effects. These drawbacks are however inherent in any steady-state procedure and are balanced by less complex technique and interpretation.

**References**


**RéSUMÉ:** La mesure et l'interprétation de la "capacité de diffusion" par les méthodes en aspée ou en état stable sont gênées par des difficultés à la fois techniques et conceptuelles. La prise fractionnelle de CO, moins complexe, est trop sujette à la ventilation de l'espace mort. Une modification de cette méthode (la prélèvement alvéolaire fractionnel du CO ou $U_{A}$) permet dans une grande mesure d'évacuer ce problème. Nous avons mesuré $U_{A}$ chez treize sujets sains et chez cent patients atteints de troubles pulmonaires divers. La méthode est reproductible et apte à reconnaître les anomalies cliniques. Sa simplicité d'utilisation et d'interprétation peut en faire une alternative aux autres mesures de transfert du CO.

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